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The relationship between brain atrophy and cognitive-behavioural symptoms in retired Canadian football players with multiple concussions

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ABSTRACT

Multiple concussions, particularly in contact sports, have been associated with cognitive deficits, psychiatric impairment and neurodegenerative diseases like chronic traumatic encephalopathy. We used volumetric and deformation-based morphometric analyses to test the hypothesis that repeated concussions may be associated with smaller regional brain volumes, poorer cognitive performance and behavioural symptoms among former professional football players compared to healthy controls. This study included fifty-three retired Canadian Football League players, 25 age- and education-matched healthy controls, and controls from the Cambridge Centre for Aging and Neuroscience database for validation. Volumetric analyses revealed greater hippocampal atrophy than expected for age in former athletes with multiple concussions than controls and smaller left hippocampal volume was associated with poorer verbal memory performance in the former athletes. Deformation-based morphometry confirmed smaller bilateral hippocampal volume that was associated with poorer verbal memory performance in athletes. Repeated concussions may lead to greater regional atrophy than expected for age.

1. Introduction

There is a high incidence of concussions, particularly among players of contact sports, with an estimated 1.6 to 3.8 million sports-related concussions occurring each year in the United States alone (Langlois et al., 1991). Professional players of contact sports will experience hits to the head but not all will report having a concussion. While most concussive events resolve within weeks, at least 10% of patients experience prolonged symptoms known as post-concussion syndrome (Hiploylee et al., 2017). Recently, there is growing concern that repeated concussions can cause late life mild cognitive impairment, an earlier onset of Alzheimer's disease (Abner et al., 2014) or the neurodegenerative disease called chronic traumatic encephalopathy (CTE) (Omalu et al., 2005; McKee et al., 2009). The majority of CTE cases have been reported in athletes involved in contact sports, including boxing, football, hockey, rugby, wrestling and soccer (Omalu et al., 2005; McKee et al., 2009; Omalu et al., 2006, 2010).

Neuronal damage from traumatic brain injury (TBI) has been

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associated with cerebral atrophy in studies of mild, moderate and severe brain injury (Shenton et al., 2012; Green et al., 2014; Cole et al., 2015). Normal aging is also associated with mild brain volume loss and some cognitive deficits (Cole et al., 2015; Bigler et al., 1997). Accelerated cognitive decline may occur as a result of mild, moderate or severe TBI, and exacerbate deficits associated with the normal aging process (Tremblay et al., 2013). Memory impairment is one of the most frequent cognitive complaints following mild, moderate and severe TBI (Rabinowitz and Levin, 2014). Verbal memory impairment may result from injury to the left medio-temporal and hippocampal regions (Frisk and Milner, 1990) while deficits in visuospatial memory may be associated with these regions in the right hemisphere (Smith and Milner, 1981). Moreover, post-concussive symptoms include behaviour and personality changes, such as depression, apathy, impulsivity and aggression (Malia et al., 1995), which have been associated with generalized and regional brain atrophy in various study populations (Matthies et al., 2012; Tajima-Pozo et al., 2015).

Several neuroimaging techniques have been used to examine whether symptoms resulting from multiple concussions are associated with smaller brain volume and impairment in function (Goswami et al., 2016; Ilvesmaki et al., 2014; Meier et al., 2016; Multani et al., 2016; Tremblay et al., 2014; Strain et al., 2015). However, results from these studies have been mixed; while some identify structural and functional brain changes associated with symptoms in both acute and chronic concussed populations (Goswami et al., 2016; Meier et al., 2016; Multani et al., 2016; Strain et al., 2015), other studies report no abnormalities (Ilvesmaki et al., 2014; Tremblay et al., 2014).

Severe, moderate and mild TBI are associated with long-term damage to the brain (McKee et al., 2009; Corsellis et al., 1973). We hypothesize that long-term damage can result from mild TBI and contribute to measurable brain atrophy and that this atrophy will be associated with cognitive deficits and behavioural changes. Using structural segmentation and deformation-based morphometry (DBM) (Ashburner et al., 1998) analyses, the current study compares the effect of multiple concussions on regional brain volumes in retired professional athletes from the Canadian Football League (ex-CFL) with non-athlete control subjects with no history of concussion. As the sample size of our control group was small, a larger control population from the Cambridge Centre for Aging and Neuroscience database was leveraged for further analysis. We also investigated the relationship between regional brain volume and memory and personality changes. We predict that ex-CFL will show greater focal atrophy of the hippocampi and amygdala, and these regions will be associated with poorer memory performance and personality changes compared to controls.

2. Materials and methods

2.1. Participants

This study included 53 ex-CFL players (mean age = 55.6 ± 12.9 years), most of whom report multiple concussions, and 25 healthy age- and education-matched male non-concussed controls (mean age = 50.8 ± 10.0 years), recruited from the general population. Athletes played for one or more seasons with the CFL. Informed consent was obtained, and the study was approved by the University Health Network research ethics board.

Age-matched male controls from the Cambridge Centre for Aging and Neuroscience (Cam-CAN, $N = 321$, mean age of 58.1 ± 16.0 years, range 30–85) were used for validation due to the small size of the local healthy control group. Data were obtained from the Cam-CAN repository (available at http://www.mrc-cbu.cam.ac.uk/datasets/camcan/) (Shafto et al., 2014; Taylor et al., 2017).

The median number of self-reported concussions in the ex-CFL group was 4 (Table 1). Exclusion criteria included: neurological disorders prior to concussions (e.g. seizure disorder), systemic illnesses known to affect the brain (e.g. diabetes and lupus), a history of psychotic disorder, known developmental disorders, and history of migraines. Similar criteria were used for study and Cam-CAN controls (Taylor et al., 2017). Concussion exposure was based on players' recall of injury during a semi-structured interview in accordance with the Zurich Guidelines on Concussions (McCrory et al., 2013). Absence of concussions in the control group was verified through interview with control subjects.

2.2. Neuropsychological assessment

All participants underwent an extensive neuropsychological test battery comprising a series of cognitive and behavioural assessments. Memory was assessed by the Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964), which is a test of verbal learning and memory; and by the Rey Visual Design Learning Test (RVDLT) (Spreen and Strauss, 1991) assessing visual learning and memory. For the RAVLT, participants were asked to repeat 15 unrelated words over five consecutive trials, after which an interference list is presented and recalled. Subjects are then asked to recall the original list after this short delay, and again after a 20-minute long delay. The number of words recalled after the short and after the long delay were the primary behavioural outcome measures. For the RVDLT, participants were presented with 15 stimulus cards with geometric design (over five consecutive trials), and asked to draw all designs they could recall after each trial. Twenty minutes after completing the final trial, participants were asked to redraw as many of the 15 designs they could recall. The number of accurately drawn figures was the primary behavioural outcome measure.

Symptoms measured by the Personality Assessment Inventory (PAI) (Morey, 1991) were included for analysis, correcting for age. The PAI was chosen to measure personality changes frequently associated with concussion. Aggression and irritability were chosen for analysis as the PAI symptoms most relevant to concussion. The PAI is a comprehensive and informative self-report questionnaire of adult personality and psychopathology, and contains 344 items scored on a 4-point scale: F = false, ST = slightly true; MT = mainly true; VT = very true. This assessment contains 22 full scales (four validity scales, 11 clinical scales, five treatment scales, and two interpersonal scales) with 10 of these scales further subdivided into 31 conceptually derived subscales. *T*-scores are based on a census matched standardization sample of 1000 normal adults.

2.3. Neuroimaging

2.3.1. Image acquisition

Participants underwent a whole-brain scan using a T1-weighted inversion recovery prepped, 3-dimensional IR-FSPGR (inversion fast spoiled gradient echo) sequence at 3 Tesla (GE Signa HDx, Milwaukee, WI, USA) with the following parameters: 180 axial slices, 1 × 1 × 1-mm voxels, 256 × 256 matrix size, 25.6-cm field of view, flip angle = 158°, echo time = 3 ms, repetition time = 7.8 ms, inversion time = 450 ms.

Cam-CAN participants underwent T1-weighted MPRAGE (magnetization prepared rapid acquisition gradient echo) sequence at 3 Tesla (Siemens TIM Trio scanner with a 32-channel head coil) with the following acquisition parameters: 1 × 1 × 1-mm voxels, field of view = 256 × 240 × 192, flip angle = 9°, echo time = 2.99 ms, repetition time = 2250 ms, inversion time = 900 ms.

2.3.2. Pre-processing

T1-weighted scans of the subjects were pre-processed through our standard pipeline. Image denoising (Coupe et al., 2008), intensity non-uniformity correction (Sled et al., 1998), and image intensity normalization into range (0 − 100) using histogram matching were performed.

2.3.3. Deformation-based morphometry

DBM analysis was performed using MNI MINC tools. Pre-processed